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Regioselective Synthesis and *ab initio* Calculations of Fused Heterocycles Thermally and under Microwave Irradiation

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Abstract

Pyrazolo[1,5-*a*]pyrimidine, triazolo[1,5-*a*]pyrimidine, and pyrimido[1,2-*a*]benzimidazole, pyrido[1,2-*a*]benzimidazole ring systems incorporating phenylsulfonyl moiety were synthesized *via* the reaction of 3-*(N*,*N*-dimethylamino)-1-(thiophen-2-yl)-2-(phenylsulfonyl)prop-2-en-1-one derivatives with the appropriate aminoazoles as 1,3-binucleophiles and 1*H*-benzimidazol-2-ylacetonitrile using conventional methods as well as microwave irradiation. The regioselectivity of the cyclocondensation reactions was confirmed both experimentally by alternative synthesis of reaction products and theoretically using *ab initio* quantum chemical calculations namely the Density Functional Theory (DFT). The theoretical work was carried out using the Becke, three parameter, Lee-Yang-Parr hybrid functional (B3LYP) combined with the 6-311++G(d,p) basis set. It was found that the final cyclocondensation reaction product depends mainly on the initial addition to the activated

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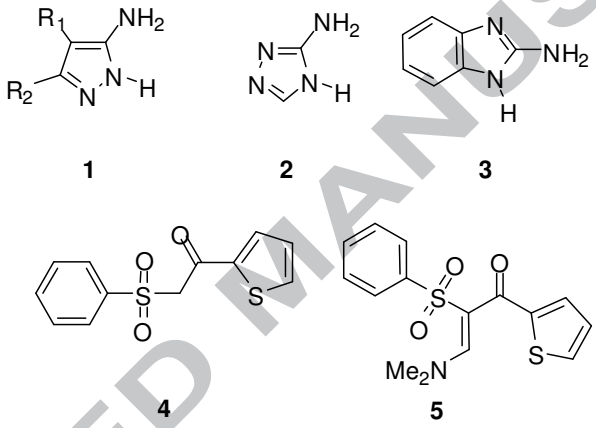
double bond by the nitrogen atom of the 1,3-binucleophiles that has the higher electron density.

Keywords: Regioselectivity; DFT calculations; Cyclocondensation; Sulfones; Alterative synthesis

Introduction

Sulfones[1-2] are a versatile class of compounds due to their applications in many pharmaceutical fields.[3-9] They have attracted the attention of many authors and great efforts have been made to develop new approaches to a variety of heterocycles incorporating phenylsulfonyl moiety for biological screening. Moreover, sulfone moiety is usually incorporated as an active part in many analgesic anti-inflammatory molecules available as drugs in the market such as celecoxib,[2,10] valdecoxib,[11] rofecoxib,[12] parecoxib,[13] etoricoxib,[14] tenoxicam,[15] piroxicam,[16] meloxicam,[17] lornoxicam,[18] ampiroxicam,[19] and nimesulide.[20,21-23] On the other hand, α-aminoazoles as 1,3-binucleophiles are quite important reagents in modern heterocyclic synthesis, and their reactions with electrophiles are the most widespread and facile synthetic approach to obtain diverse fused heterocyclic systems containing azole moiety.[24-26] In addition, aminoazoles and their ambident properties make them challenging objectives for studying mechanisms of organic reactions and then tuning their regioselectivity. The mostly investigated area of aminoazoles chemistry is their two component reactions with ketoesters, β-dicarbonyls, α,β-unsaturated aldehydes/ketones and enaminones yielding fused azoloazines.[24-31] Moreover, multicomponent reactions (MCRs) based on aminoazole building-blocks were covered in literature which are very promising for combinatorial and medicinal chemistry as well as for diversity-oriented synthesis.[32] In continuation of our recent work aiming at the synthesis of heterocyclic systems with remarkable biological importances,[33-38] the utility of β-keto-β-sulfonylenamines as building blocks for the synthesis of pyrazolo[1,5-*a*]pyrimidines, 1,2,4-triazolo[1,5-*a*]pyrimidines,

pyrimido[1,2-*a*]benzimidazole, and pyrido[1,2-*a*]benzimidazole under microwave irradiation is reported. In this work, several aminoazoles as 1,3-binucleophiles, namely; 5-amino-1*H*-pyrazoles **1**, 3-amino-1,2,4-triazole (**2**), and 2-aminobenzimidazole (**3**) are used in construction of the corresponding fused ring systems via their cyclocondensation with enaminosulfone, (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)-prop-2-en-1-one (**5**) as well as their MCR with the sulfone, 2-phenylsulfonyl-1-(thiophen-2-yl)-ethan-1-one (**4**) and triethyl orthoformate as a CH-acid.

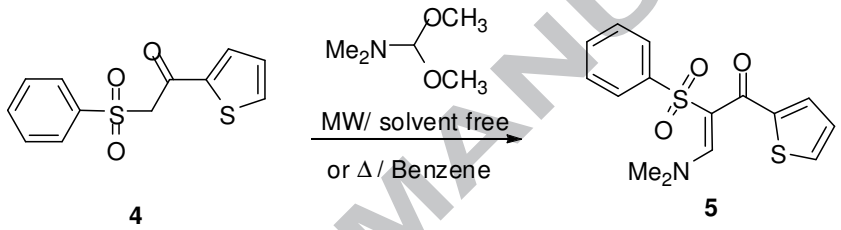


The regioselectivity in such cyclocondensation reaction was examined using DFT quantum chemical calculations. Geometry optimizations have been performed for heterocyclic amines **1**, **2**, **3**, and the enaminosulfone **5**. The molecular geometries were fully optimized using the gradient minimization technique. The minima are characterized by having zero gradient norms and by diagonalizing the matrix of the second derivatives to give positive harmonic vibrational frequencies. This was done using the Becke, three parameter, Lee-Yang-Parr hybrid functional (B3LYP)[39] combined with the 6-311++G(d,p) basis set.[40] These calculations have been performed using the Gaussian09 program package.[41] The partial atomic charges on the first nucleophilic center N of NH_2 and the second nucleophilic center

N of NH are calculated using Mulliken population analysis, atomic polar tensor (APT), and electrostatic potential (ESP).

Results and discussion

The versatile, *hitherto* unreported (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)-prop-2-en-1-one (**5**) was readily obtained by refluxing equimolar quantities of 2-phenylsulfonyl-1-(thiophen-2-yl)-ethan-1-one (**4**) and dimethylformamide dimethylacetal (DMF-DMA), without solvent under microwave irradiation or in benzene under conventional method as shown in scheme 1.



4 **5**

Thermal Yield 80%
MW Yield 95%

Scheme 1

The structure of the enaminosulfone **5** was confirmed by its elemental analysis and spectral data. For example, its ^{1}H NMR spectrum displayed a singlet signal at δ 3.33 due to *N,N*-dimethyl protons, a singlet signal at δ 7.91 due to olefinic proton, in addition to an aromatic and thiophene ring multiplets in the region δ 7.15-7.96.

The reactivity of the enaminosulfone **5**, in general, can be attributed to the delocalization of the lone pair of electrons on NMe_2 nitrogen (N) with the carbonyl carbon (C) as well as the conjugation with the sulfone group, see Fig. 1. These delocalization and conjugation effects result in two electron poor centers at N and C between which an electron rich carbon atom.

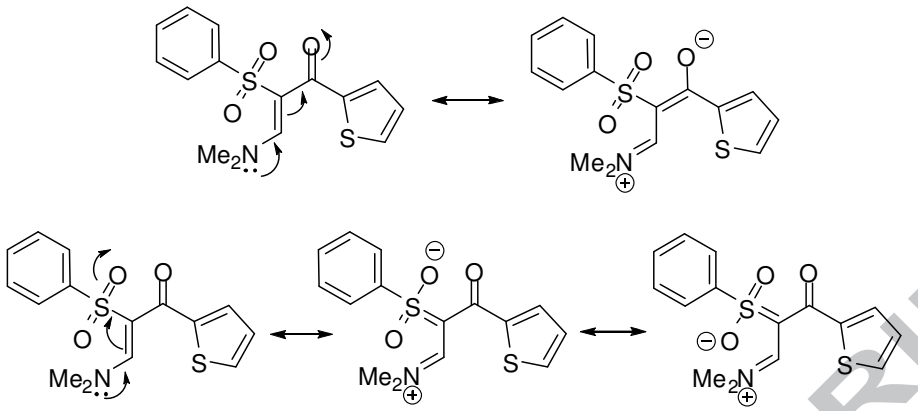
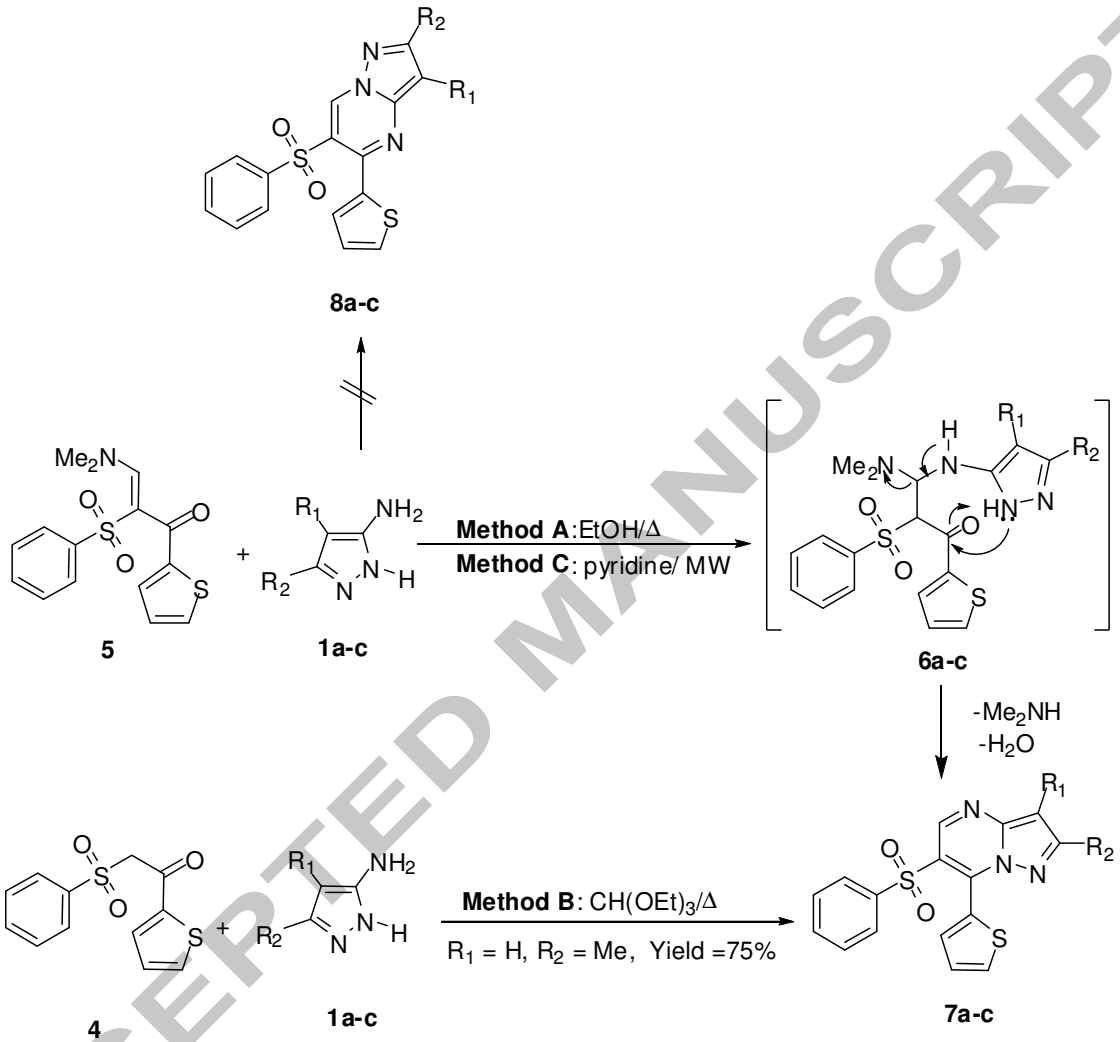


Fig. 1. The tautomeric forms of the enaminosulfone (5).

When (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)-prop-2-en-1-one (**5**) was treated with substituted 5-amino-1*H*-pyrazole derivatives **1a-c,** either under refluxing ethanol in the presence of a catalytic amount of piperidine or in pyridine under MW irradiation, it afforded, the corresponding 6-(phenylsulfonyl)-7-(thien-2-yl)pyrazolo[1,5-*a*]pyrimidine derivatives **7a-c** (Scheme 2) in a good yield as shown in Table 1. In general, the yields of the microwave synthesis are higher than the conventional heating as expected. The structures of **7a-c** were established on the basis of their elemental analyses and spectral data. For example, the mass spectrum of compound **7a**, revealed a molecular ion peak at *m/z* 451. Its ^{1}H NMR spectrum revealed a singlet signal at δ 7.52 due to pyrazole CH-3 proton and a singlet signal at δ 9.18 (pyrimidine-CH-5), in addition to aromatic protons as a multiplet at δ 7.25-8.02. The formation of **7a-c** is assumed to take place *via* an initial *Michael-type* addition of the exocyclic amino group in aminopyrazoles **1a-c** to *α,β*-unsaturated moiety in the enaminosulfone **5,** to yield the corresponding acyclic non-isolable intermediates **6a-c** which undergo intramolecular cyclization and aromatization into the final products **7a-c** under the reaction conditions (Scheme 2). The other expected product **8a-c** was ruled out on the basis of alternative synthesis of compounds **7a-c** theoretical investigations. Thus, solvent free one-pot, three component reaction of the sulfone **4**, aminopyrazoles **1b** (taken as a typical

example), and triethyl orthoformate, afforded product identical in all respects (m.p., mixed m.p. and IR spectra) with the product obtained from the stepwise synthesis (Scheme 2).



7	R_1	R_2	Δ Yield %	MW Yield %
7a	H	C_6H_4Cl-*p*	65	80
7b	H	CH_3	67	81
7c	Me	C_6H_5	68	87

Scheme 2

DFT calculations show that the electron density on the first nucleophilic center, N of NH_2 ($N_{exocyclic}$), is more than that on the second nucleophilic center, N of NH ($N_{endocyclic}$), for the optimized structure of aminopyrazole **1** (Fig. 2). This is valid for the three different types of the population analyses, which have charges ratios of $N_{exocyclic}$ to $N_{endocyclic}$ nucleophilic centers range from 2.0 to 4.9 (see Table 1). This leads the aminopyrazole **1** to attack the enaminosulfone **5** (Fig. 3) *via* $N_{exocyclic}$ nucleophilic center producing 6-(phenylsulfonyl)-7-(thien-2-yl)pyrazolo[1,5-*a*]pyrimidine derivatives **7a-c**. This can be elucidated through analyzing the highest occupied molecular orbital (HOMO) of aminopyrazoles **1** (Fig. 2) where the electron density on $N_{exocyclic}$ nucleophilic center is more than that on $N_{endocyclic}$.

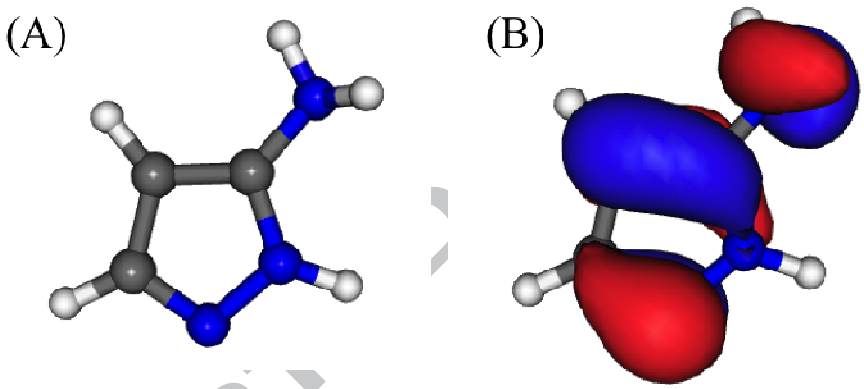


Fig. 2. The optimized three-dimensional structure (A) and HOMO (B) for the compound **1**.

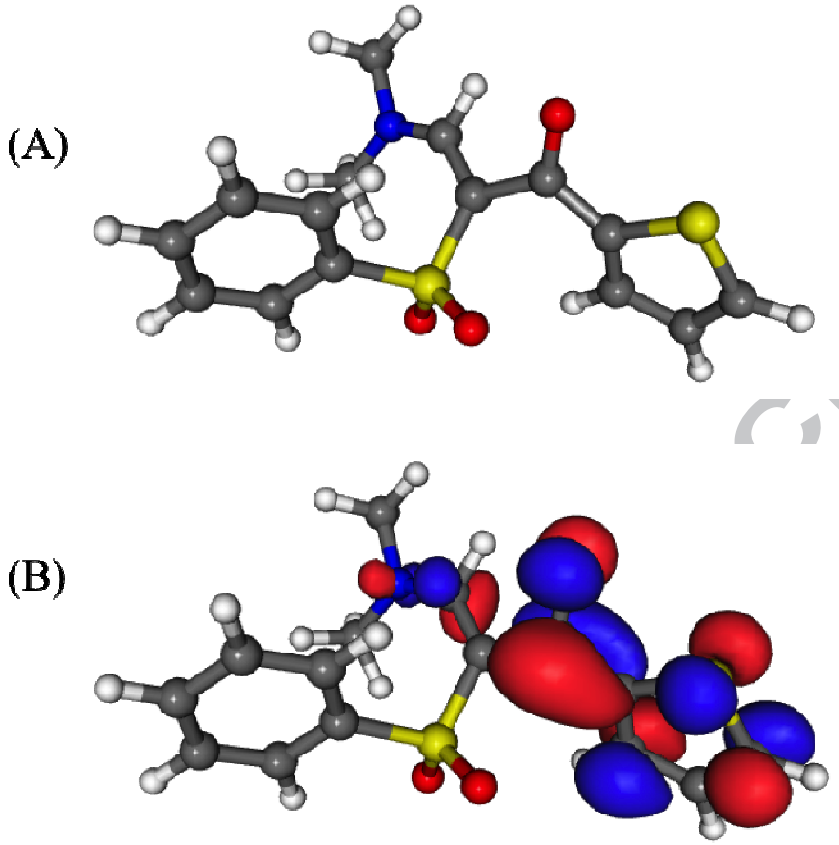
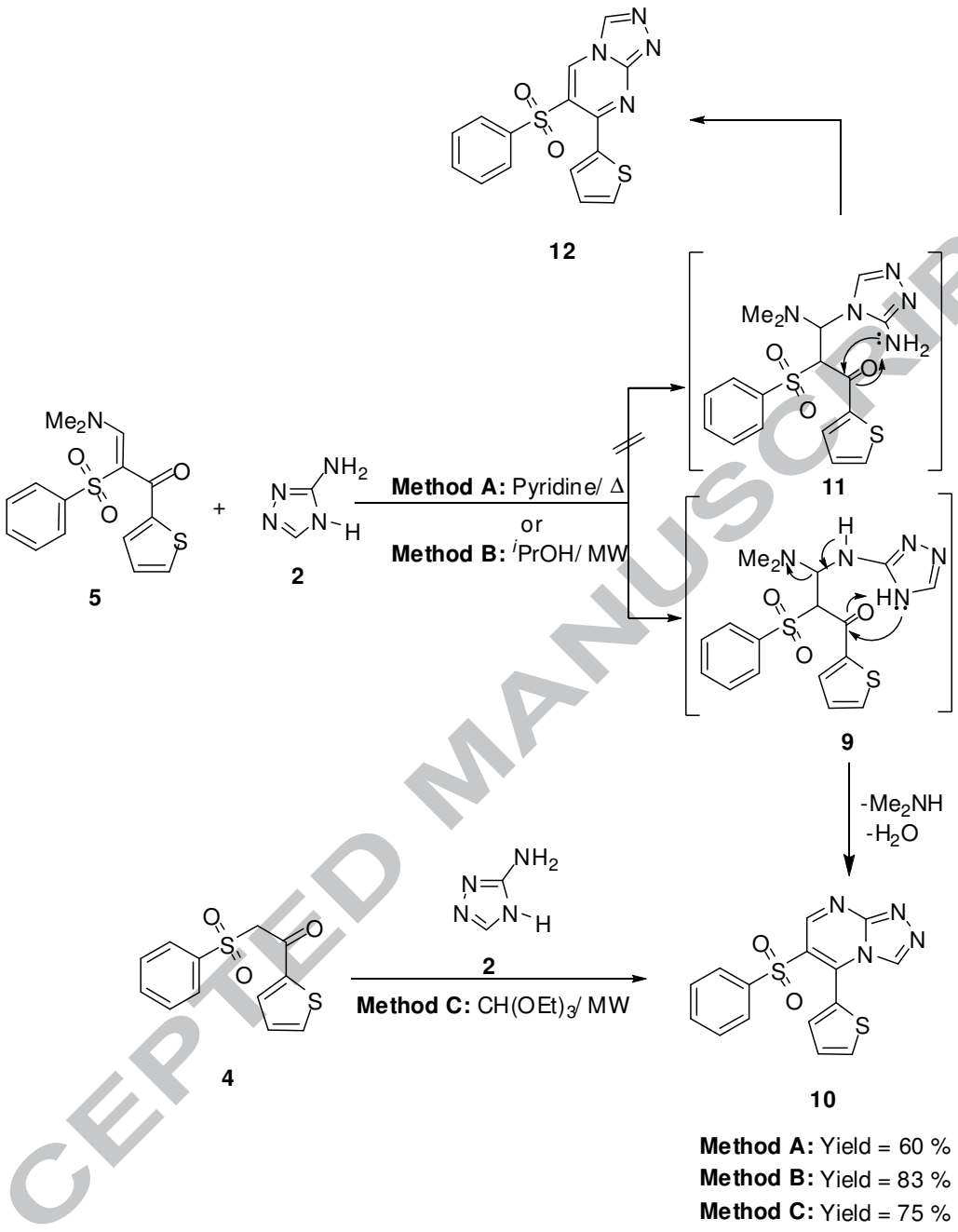


Fig. 3. The optimized three-dimensional structure (A) and the lowest unoccupied molecular orbital (LUMO), (B), for the compound **5**.

Table 1: Different types of partial atomic charges, for compounds **1**, **2**, and **3,** of the first and second nucleophilic centers and their ratios.

		atomic charge			$N_{exocyclic}/N_{endocyclic}$ charges ratio		
		Mulliken	APT	ESP	Mulliken	APT	ESP
compound **1**	$N_{exocyclic}$	-0.353	-0.586	-1.034	3.530	1.993	4.924
	$N_{endocyclic}$	-0.100	-0.294	-0.210			
compound **2**	$N_{exocyclic}$	-0.327	-0.607	-0.882	1.086	1.412	1.696
	$N_{endocyclic}$	-0.301	-0.430	-0.520			
compound **3**	$N_{exocyclic}$	-0.340	-0.771	-0.872	1.232	1.369	1.235
	$N_{endocyclic}$	-0.276	-0.563	-0.706			

Reaction of enaminosulfone **5** with 3-amino-1,2,4-triazole (**2**), in refluxing pyridine or under microwave irradiation, afforded the corresponding 6-(phenylsulfonyl)-7-(thien-2-yl)-1,2,4-triazolo[1,5-*a*]pyrimidine (**10**) (Scheme 3). The ^{1}H NMR spectrum of the latter revealed a singlet signal at δ 10.00 (triazole-CH-2) and a singlet signal at δ 8.91 (pyrimidine-CH-5), in addition to aromatic protons as a multiplet in the region δ 7.12-7.87. The IR spectrum of the same compound showed the absence of a band corresponding to carbonyl absorption. A plausible mechanism for the formation of **10** is outlined in Scheme 3.



Scheme 3

The product **10** is assumed to be formed *via* an initial *Michael-type* addition of the amino group of **2** ($N_{exocyclic}$) to the activated double bond in the enaminosulfone **5** followed by elimination of dimethylamine and water molecules, from the non-isolable intermediate (**9**), to afford the final product **10** as shown in Scheme 3. This proposed mechanism is in agreement

with the theoretical findings, where, according to ESP, the electron density on $N_{exocyclic}$ nucleophilic center is more than that on $N_{endocyclic}$ nucleophilic center for the optimized structure of (**2**) (charges ratio of first nucleophilic center to second one is 1.7), see Table 1 and Fig. 4. This directs aminotriazole **2** to bind the enaminosulfone **5** through $N_{exocyclic}$ nucleophilic center yielding 6-(phenylsulfonyl)-7-(thien-2-yl)-1,2,4-triazolo[1,5-*a*]pyrimidine (**10**).

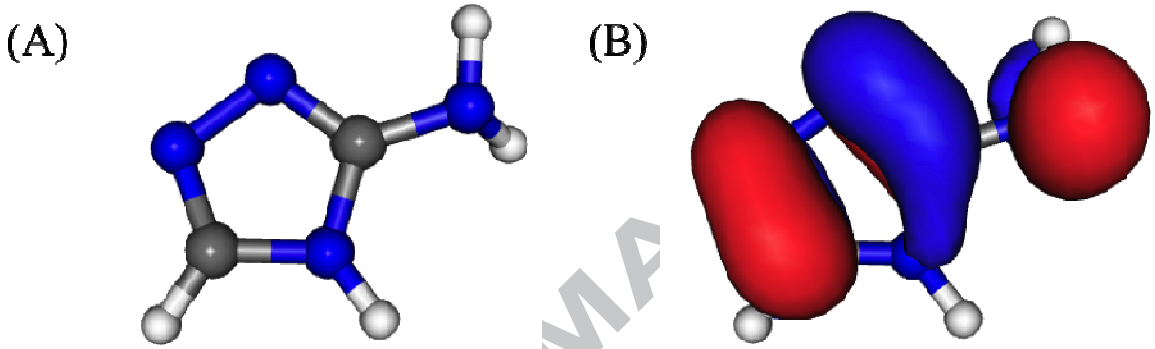
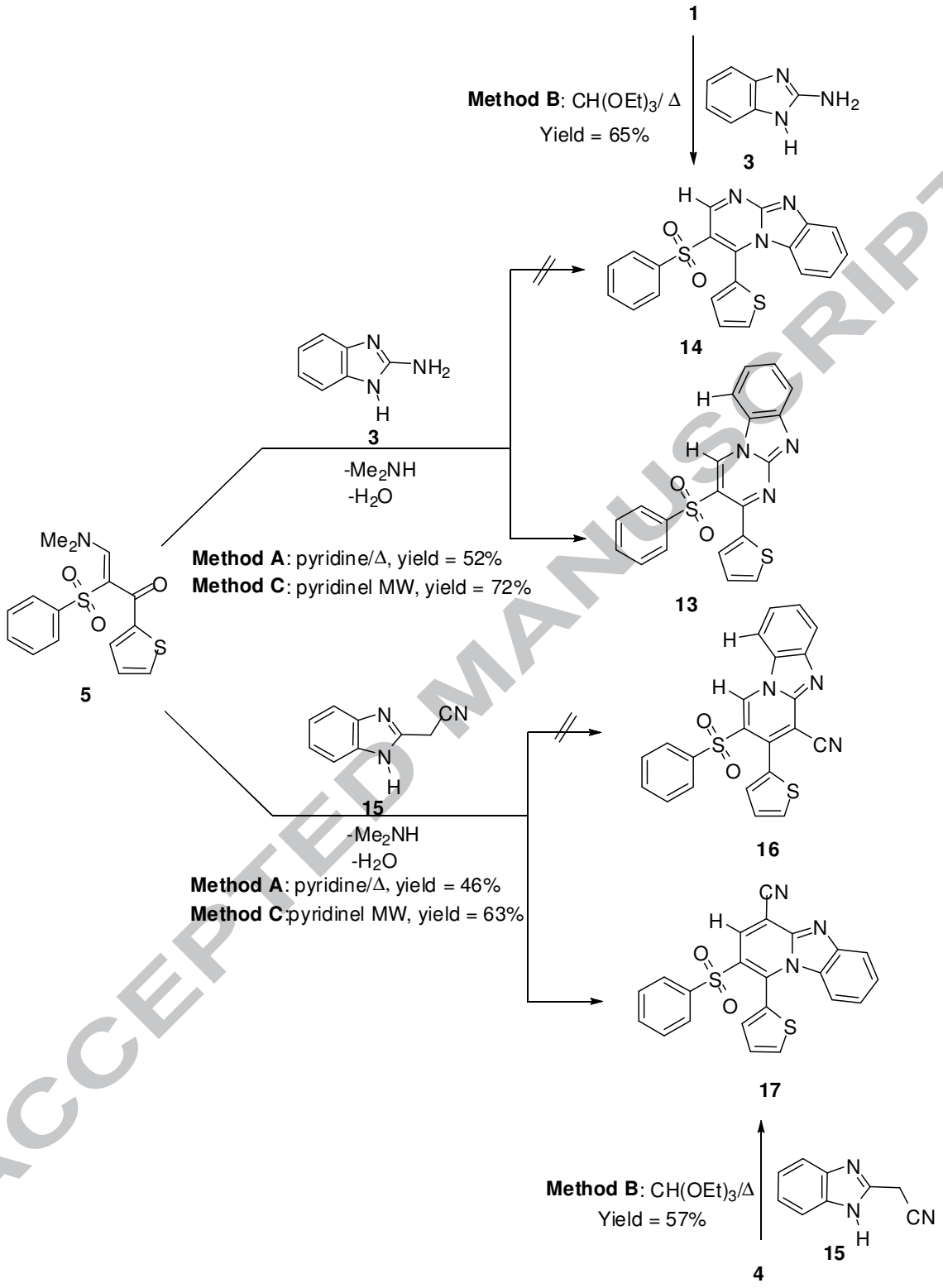


Fig. 4. The optimized three-dimensional structure (A) and HOMO for aminotriazole (**2**).

In order to confirm this regioselectivity through alternative synthesis, the sulfone **4** was allowed to react with aminotriazole **2**, and triethyl orthoformate as one pot solvent free reaction. The obtained product was found to be identical in all respects (m.p., mixed m.p. and IR spectrum) with the product **10** obtained from the stepwise synthesis (Scheme 3).

In contrast to its behavior towards the aminopyrazole derivatives **1a-c** and 3-amino-1,2,4-triazole (**2**), the enaminosulfone **5** reacts with 2-aminobenzimidazole (**3**) in refluxing pyridine under microwave irradiation or under conventional heat to afford only one isolable product (as examined by TLC). The reaction product was identified as 3-(thiophen-2-yl)-2-phenylsulphonylpyrimido[1,2-*a*]benzimidazole (**13**) (Scheme 4).



Scheme 4

The spectral data of the isolated product **13** are in complete agreement with the assigned structure. For example, its IR spectrum revealed no bands due to amino or carbonyl functions. Moreover, its ^{1}H NMR spectrum revealed an aromatic multiplet in the region δ 7.11-8.63, in addition to a singlet signal at δ 10.30 due to pyrimidine-CH-1.

The formation of compound **13** is assumed to take place *via* an initial *Michael-type* addition of the imino function ($N_{endocyclic}$) in compound **3** to the double bond in the enaminone **5** as shown is (Scheme 4). Theoretical calculations show that the electron density on the first nucleophilic center is comparable to that on the second nucleophilic center for the optimized structure of 2-aminobenzimidazole **3**. For ESP, charges ratio of first nucleophilic center to second one is 1.2. This small atomic partial charges difference between the first and the second nucleophilic centers, disable our decision for the direction of the reaction. Therefore, it is important to look deeply for the HOMO of 2-aminobenzimidazole **3**, which is responsible for electron donation. Fig. 5 shows that the electron density is close to the second nucleophilic center (NH) than the first one (NH_2). This enhances the attack v*ia* the second nucleophilic center of 2-aminobenzimidazole (**3**) to the enaminosulfone **5** yeilding 3-(thiophen-2-yl)-2-phenylsulphonyl pyrimido[1,2-*a*]benzimidazole (1**3**).

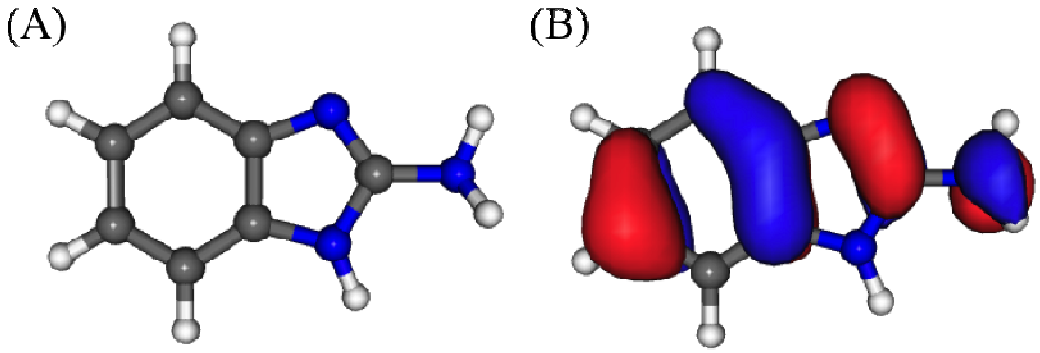


Fig. 5. The optimized three-dimensional structure (A) and HOMO for compound 2-aminobenzimidazole (**3**).

The cyclocondensation product **14** could be obtained by solvent free one pot three component reaction of the sulfone **4**, 2-aminobenzimidazole (**3**) and triethyl orthoformate as shown in Scheme 4. The reaction product was identified as 3-(phenylsulfonyl)-2-(thiophen-2-yl) pyrimido[1,2-*a*]benzimidazole (**14**) (Scheme 4). The spectral data of the isolated product **14** are in complete agreement with the assigned structure. For example, its IR spectrum revealed no bands due to amino or carbonyl functions. Moreover, its ^{1}H NMR spectrum revealed an aromatic multiplet in region δ 5.88-8.10, in addition to a singlet signal at δ 9.41 (pyrimidine-CH-1). The difference between the structures **13** and **14** is distinguishable from the values of the chemical shifts of the pyrimidine-CH where the structure **14** showed higher value (δ 10.30) than that of other possible regioisomer **13** which may be attributed to the magnetic anisotropy effect of the adjacent benzene ring as shown in the Fig. 6.

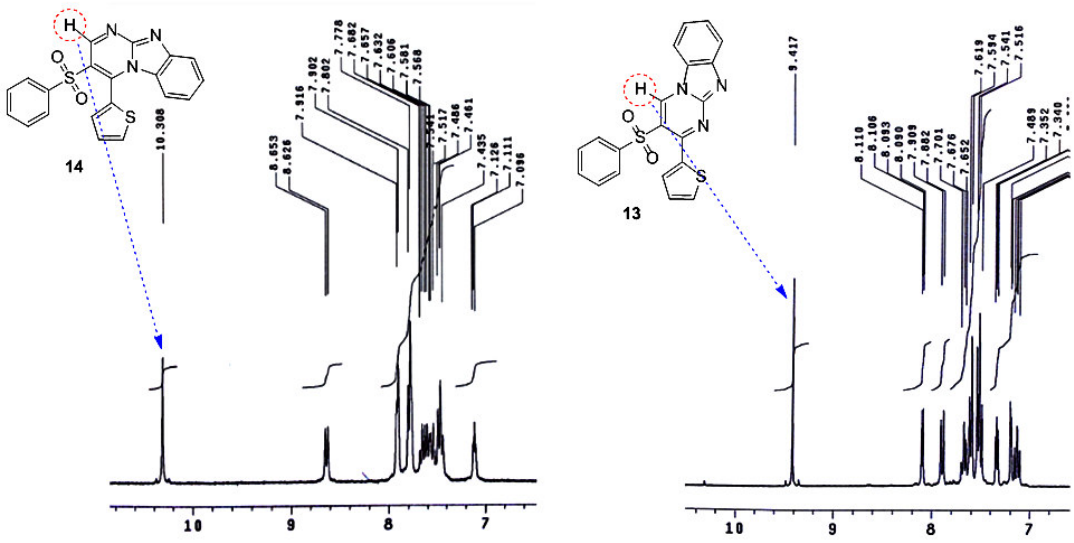


Fig.6. Aromatic region of the ^{1}H NMR spectra of regioisomers **13** and **14.**

In similar manner, the enaminosulfone **4** reacts with 1*H*-benzimidazol-2-yl acetonitrile (**15**), in refluxing pyridine, to afford only one isolable product identified as 3-(thiophen-2-yl)-2-phenylsulphonylpyrido[1,2-*a*]benzimidazole-4-carbonitrile (**16**) and not the other possible regioisomer **17** (Scheme 4).

The structure of reaction product **16** was assigned on the basis of its elemental analysis and spectral data. For example, its IR spectrum exhibited a characteristic absorption band at 2130 cm^{-1} due to a nitrile function and revealed the absence of absorption band corresponding to carbonyl group. Moreover, its ^{1}H NMR spectrum revealed an aromatic multiplet in region δ 5.89-8.07, in addition to a singlet signal at δ 8.93 (pyridine-CH-4). These results ruled out the existence of the other isomeric product which contain pyridine-CH-2. The latter expected to resonate at higher chemical shifts as shown in Fig. 7.

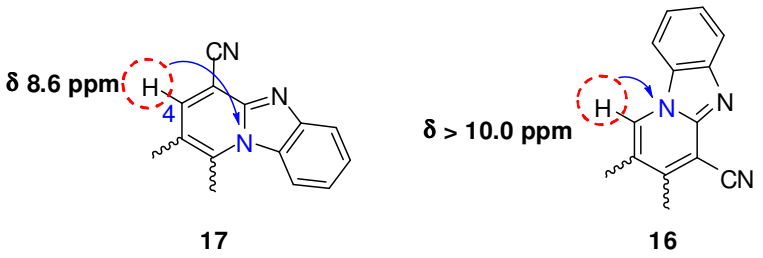


Fig. 7. Comparison between pyridine-2-CH and pyridine-4-CH protons chemical shifts in the regioisomers **16** and **17**.

Also, the other expected product **17** was ruled out on the basis of an alternative synthesis of compound **16**. Thus, solvent free one pot three component reaction of the sulfone **1**, 1*H*-benzimidazol-2-ylacetonitrile (**15**), and triethyl orthoformate, afforded product identical in all respects (m.p., mixed m.p. and IR spectra) with the product **15** obtained from the stepwise synthesis (Scheme 4).

Experimental

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide discs on a Pye Unicam SP 3–300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VXR-300 NMR spectrometer (^{1}H NMR (300 MHz) and ^{13}C NMR (75.46 MHz)) were run in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro-analytical Centre of Cairo University, Giza, Egypt and recorded on Elementar-Vario EL automatic analyzer. Microwave irradiation was performed using the Discover system of CEM.

Synthesis of (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)prop-2-en-1-on (5)

Thermal method

To a solution of 2-(Phenylsulfonyl)-1-(thiophen-2-yl)ethanone (**4**) (26.6 g, 100 mmole) in dry benzene (150 ml) was added dimethylformamide-dimethylacetal *(DMF-DMA)* (11.9 g, 100 mmol) and the mixture was refluxed for 8 h. The solvent was distilled off under reduced pressure and the residual reddish brown viscous liquid was taken in petroleum ether (20 ml) and the resulting orange crystal was collected by filtration, washed thoroughly with ether, dried and finally recrystallized from dry benzene to afford the (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)prop-2-en-1-one (**5**) in (80% yield), m.p 150°C.

Microwave method (MW)

To a solution of 2-(Phenylsulfonyl)-1-(thiophen-2-yl)ethanone (**4**) (2.66 g, 10 mmole) was added dimethylformamide-dimethylacetal *(DMF-DMA)* (11.9 g, 100 mmol) and the mixture was mixed in a process vial. The vial was capped properly and irradiated by microwaves under pressurized conditions (17.2 bar, 110 °C) for 20 min. The reaction mixture was evaporated in *vacuo* and the residual solid was taken in ether, washed with ether and dried and finally recrystallized from dry benzene to afford the (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)prop-2-en-1-one (**5**) in (95% yield), m.p 150°C, The physical and spectral data of the synthesized compound are listed below.

IR (KBr) ν_{max}/cm^{-1}: 1655 (C=O), 1585 (C=N). 1H NMR (DMSO-d_6): δ 3.33 (s, 6H, $N(CH_3)_2$), 7.15 (d, 1H), 7.48-7.57 (m, 4H, ArH's), 7.78 (d, 2H, ArH's), 7.91 (s, 1H, =CH-N), 7.96 (d, 1H, ArH), . MS (m/z): 321 (M^+). Analysis for $C_{15}H_{15}NO_3S_2$: Calcd: C, 56.05; H, 4.70; N, 4.36. Found: C, 56.19; H, 4.51; N, 4.20%

Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives (7a-c)

Thermal methods:

Method A

General procedure:

To a mixture of (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)prop-2-en-1-one (**5**) (3.21 g, 10 mmol) and the appropriate aminopyrazole derivative **1a-c** (10 mmol), in absolute ethanol (25 ml), few drops of piperidine was added and the reaction mixture was refluxed for 6h then left to cool. The solid product was filtered off, washed with ethanol and recrystallized from EtOH/DMF to afford the corresponding pyrazolo[1,5-*a*]pyrimidine derivatives **7a-c** in 65-68% yield.

Method B

General procedure:

A solution of sulfone (**4**) (3.21 g, 10 mmol) and an equivalent molar ratio of the appropriate aminopyrazole derivative **1a-c** and triethyl orthoformate (10 mL), was heated under reflux for 4 h. The excess triethyl orthoformate was removed by distillation under reduced pressure and the residue was left to cool. The precipitated solid product was collected by filtration, washed with ethanol, dried and finally recrystallized from DMF/EtOH to afford the corresponding pyrazolo[1,5-*a*]pyrimidine derivatives **7a-c**, respectively.

Microwave method (MW):

Method C

General procedure:

A mixture of the enaminosulfone **5** (3.21 g, 10 mmol) and the appropriate aminopyrazole derivative **1a-c** (10 mmol) in pyridine (10 ml) was mixed in a process vial. The vial was capped properly and irradiated with microwaves under pressurized conditions (17.2 bar, 130 ^{o}C) for 20 min. The reaction mixture was evaporated in *vacuo* and the residual solid was

taken in ethanol, filtered off and dried and finally recrystallized from DMF/EtOH to afford the corresponding pyrazolo[1,5-*a*]pyrimidine derivatives **7a-c** in 80-87% yield.

2-(4-Chlorophenyl)-6-(phenylsulfonyl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (7a)

Yield 70%; mp. 248-250˚C. IR (KBr) ν_{max} /cm^{-1}: 1607 (C=N). ^{1}H NMR (DMSO-d_6): δ 7.25 (d, 1H, ArH), 7.44 (t, 2H, ArH's), 7.51-7.62 (m, 5H, ArH's), 7.52 (s, 1H, pyrazole-3-CH), 7.95 (d, 2H, ArH's), 8.02 (d, 2H, ArH's), 9.18 (s, 1H, pyrimidine-5-CH). MS (*m/z*): 451 (M^+, 100%), 453 (M^++2, 45%). Analysis for $C_{22}H_{14}ClN_3O_2S_2$: Calcd: C, 58.47; H, 3.12; N, 9.30 % Found: C, 58.24; H, 3.01; N, 9.65%

2-Methyl-6-(phenylsulfonyl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (7b)

Yield 68%; mp. 251-253˚C. IR (KBr) ν_{max} /cm^{-1}: 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 6.79 (s, 1H, pyrazole-3-CH), 7.20 (d, 1H, ArH), 7.39-7.49 (m, 5H, ArH's), 7.58 (t, 1H, ArH), 7.95 (d, 1H, ArH), 9.11 (s, 1H, pyrimidine-5-CH). MS (*m/z*): 355 (M^+, 100%). Analysis for $C_{17}H_{13}N_3O_2S_2$: Calcd: C, 57.45; H, 3.69; N, 11.82. Found: C, 57.39; H, 3.61; N, 11.68%

3-Methyl-2-phenyl-6-(phenylsulfonyl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (7c)

Yield 69%; mp. 220-221˚C. IR (KBr) ν_{max} /cm^{-1}: 1604 (C=N). ^{1}H NMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3), 7.22 (d, 1H, ArH), 7.37-7.53 (m, 9H, ArH's), 7.62 (t, 1H, ArH), 7.70 (d, 1H, ArH), 7.98 (d, 1H, ArH), 9.16 (s, 1H, pyrimidine-5-CH). MS (*m/z*): 431 (M^+, 100%). Analysis for $C_{23}H_{17}N_3O_2S_2$: Calcd: C, 64.02; H, 3.97; N, 9.74. Found: C, 64.19; H, 3.81; N, 9.68%

Synthesis of triazolo[1,5-*a*]pyrimidine derivative (10)

Thermal method:

Method A

To a mixture of (E)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)prop-2-en-1-one (**5**) (3.21 g, 10 mmol) and 3-amino-l,2,4-triazole **(2)** (10mmol) in pyridine (25 ml) was refluxed for 12 h, then left to cool. The excess pyridine was evaporated in *vacuo* and the residual solid was taken in ethanol then collected by filtration, washed several times with water, dried and finally recrystallized from DMF/H_2O to afford the corresponding triazolo[1,5-*a*]pyrimidine (**10**).

Microwave methods (MW):

Method B

A mixture of the enaminosulfone **5** (3.21g, 10 mmol) and 3-amino-l,2,4-triazole (**2**) in isopropyl alcohol (10 ml) was mixed in a process vial. The vial was capped properly and irradiated with microwaves under pressurized conditions (17.2 bar, 90 ^{o}C) for 20 min. The reaction mixture was evaporated in *vacuo* and the residual solid was taken in ethanol, filtered off and dried and finally recrystallized from ethanol to afford the corresponding triazolo[1,5-*a*]pyrimidine (**10**).

Method C

A mixture of the sulfone **4** (3.21g, 10 mmol) and 3-amino-l,2,4-triazole (**2**) and triethyl orthoformate (10 mL) was mixed in a process vial. The vial was capped properly and irradiated with microwaves under pressurized conditions (17.2 bar, 100 ^{o}C) for 20 min. The reaction mixture was evaporated in vacuo and the residual solid was taken in ethanol, filtered off and dried and finally recrystallized from ethanol to afford the corresponding triazolo[1,5-*a*]pyrimidine (**10**).

6-(Phenylsulfonyl)-7-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (10)

Yield 74%; mp. 280-282 °C. IR (KBr) ν_{max} /cm^{-1}: 1612 (C=N). ^{1}H NMR (DMSO-*d6*): δ 7.12 (d, 1H, ArH), 7.44(t, 2H, ArH's), 7.74 (m, 4H, ArH's), 7.87 (d, 1H, ArH), 8.91 (s, 1H, pyrimidine-5-CH),10.00 (s, 1H, triazole-2-CH). MS (*m/z*): 342 (M^+, 100%). Analysis for $C_{15}H_{10}N_4O_2S_2$: Calcd: C, 52.62; H, 2.94; N, 16.36. Found: C, 52.42; H, 2.99; N, 16.47%

Synthesis of pyrimido[1,2-*a*]benzimidazoles 13, 14 and pyrido[1,2-*a*]benzimidazole derivative (**17**)

(A)-Thermal method:

Method A

General procedure:

To a mixture of (*E*)-3-(dimethylamino)-2-(phenylsulfonyl)-1-(thiophen-2-yl)prop-2-en-1-one (**5**) (3.21 g, 10 mmol) and the appropriate 2-aminobenzimidazole **(3)** or 2-cyano-methylbenzimidazole **(15)** (10mmol) in pyridine (25 ml) was refluxed for 12 h, then left to cool. The solvent was evaporated in *vacuo* and the residual solid was taken in ethanol then collected by filtration, washed with water, dried and finally recrystallized from DMF/H_2O to afford the corresponding pyrimido[1,2-*a*]benzimidazole or pyrido[1,2-*a*]benzimidazole derivatives (**13**) and (**17**), respectively.

Method B

A solution of and 2-aminobenzimidazole (**3**) or 2-cyano-methylbenzimidazole **(15)** (10mmol) in triethyl orthoformate (10 mL) and sulfone (**4**) (10 mmol) was heated under reflux for 6 h. The excess triethyl orthoformate was removed by distillation under reduced pressure and the residue was left to cool. The precipitated solid product was collected by filtration, washed with ethanol, dried and finally recrystallized from DMF/ H_2O to afford the corresponding pyrimido[1,2-*a*]benzimidazole and pyrido[1,2-*a*]benzimidazole derivatives (**14**) and (**17**), respectively.

(B)-Microwave method (MW):

General procedure:

A mixture of the enaminosulfone **5** (3.21 g, 10 mmol) and the appropriate 2-aminobenzimidazole (**3**) or 2-cyano-methylbenzimidazole (**15**) (10 mmol) in pyridine (10 ml) was mixed in a process vial. The vial was capped properly and irradiated with microwaves under pressurized conditions (17.2 bar, 130 ^{o}C) for 20 min. The reaction mixture was evaporated in *vacuo* and the residual solid was taken in ethanol, filtered off and dried and finally recrystallized from ethanol to afford the corresponding pyrimido[1,2-*a*]benzimidazole or pyrido[1,2-*a*] benzimidazole derivatives (**13**) and (**17**), respectively. The physical and spectral data of the synthesized compounds (**13**)**,** (**14**) and (**17**) are listed below

3-(Phenylsulfonyl)-4-(thiophen-2-yl)pyrimido[1,2-*a*]benzimidazole (**13**)

Yield 81%; mp. 225 ˚C. IR (KBr) ν_{max} /cm^{-1}: 1620 (C=N). ^{1}H NMR (DMSO-*d6*): δ 7.11 (d, 1H, ArH), 7.43 (t, 2H, ArH's), 7.51-7.89 (m, 6H, ArH's), 7.90 (d, 1H), 7.92 (d, 1H, ArH), 8.64 (d, 1H, ArH), 10.30 (s, 1H, pyrimidine-1-CH). MS (*m/z*): 391 (M^+, 99%). Analysis for $C_{20}H_{13}N_3O_2S_2$: Calcd: C, 61.36; H, 3.35; N, 10.73. Found: C, 61.52; H, 3.22; N, 10.57%

3-(phenylsulfonyl)-2-(thiophen-2-yl) pyrimido[1,2-*a*]benzimidazole (**14**)

Yield 81%; mp. 268 ˚C. IR (KBr) ν_{max} /cm^{-1}: 1622 (C=N). ^{1}H NMR (DMSO-*d6*): δ 5.88 (d, 1H), 7.10 (t, 1H, ArH), 7.13 (d, 1H, ArH), 7.34 (t, 1H, ArH), 7.48 (t, 2H, ArH's), 7.60 (d, 1H, ArH), 7.67 (t, 2H, ArH's), 7.89 (d, 1H, ArH), 8.10 (d, 1H, ArH), 9.41 (s, 1H, pyrimidine-1-CH). MS (*m/z*): 391 (M^+, 99%). Analysis for $C_{20}H_{13}N_3O_2S_2$: Calcd: C, 61.36; H, 3.35; N, 10.73. Found: C, 60.12; H, 3.32; N, 10.57%

2-(Phenylsulfonyl)-3-(Thiophen-2-yl)pyrido[1,2-*a*]benzimidazole-4-carbonitrile (**17**)

Yield 85%; mp. 240 °C. IR (KBr) ν_{max}/cm^{-1}: 2130 (C≡N), 1615 (C=N). ^1H NMR (DMSO-*d6*): δ 5.89 (d, 1H), 7.11-7.13 (m, 4H, ArH's), 7.32 (t, 1H, ArH), 7.50-7.59 (m, 2H, ArH's), 7.66 (t, 1H, ArH), 7.81 (d, 1H, ArH), 7.97 (t, 1H, ArH), 8.07 (d, 1H, ArH) 8.93 (s, 1H, pyridine-1-CH). MS (*m/z*): 415 (M^+, 100%). Analysis for $C_{22}H_{13}N_3O_2S_2$: Calcd: C, 63.60; H, 3.15; N, 10.11. Found: C, 63.62; H, 3.02; N, 10.33%

Conclusions

In conclusion we synthesized a variety of fused heterocyclic systems consolidating phenylsulfonyl moiety *via* the reaction of 3-*(N,N*-dimethylamino)-1-(thiophen-2-yl)-2-(phenylsulfonyl)prop-2-en-1-one derivatives with the suitable 1,3-binucleophiles using conventional methods as well as microwave irradiation. Furthermore, a theoretical account on the regioselectivity of the cyclocondensation reactions was carried out using DFT concerted with B3LYP/6-311++G(d,p) combination. The newly synthesized fused heterocycles encompass the advantage that they can be easily synthesized on large scales from inexpensive starting materials and we believe that they are useful compounds with potentially high pharmacological and biological activities. This contribution pinpoints that the final cyclocondensation reaction product relied essentially on the nitrogen electron density of the 1,3-binucleophiles that initially attacks the activated double bond.

Supporting information (SI)

Electronic Supporting Information (SI) is available including the original NMR charts of compounds **5, 7a-c, 10, 13, 14** and **17**.

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Highlights

- Biologically important heterocyclic systems have been synthesized from inexpensive starting materials.
- Microwave irradiation in addition to the conventional methods have been used in the synthesis.
- The regioselectivity of this cyclocondensation reaction has been revealed by DFT calculations.
- The reaction product is dependent on the nitrogen electron density of the 1,3-binucleophiles.